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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,600	01/10/2002	Frederic Triebel	TRIEBEL=2A	5099

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,600	TRIEBEL, FREDERIC	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/9/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgment is made of applicants election of the species LAG-3 in the Paper filed August 3, 2004. After review and consideration of the prior art, the invention as pertaining to CD4 was also included.

2. Claims 1-9 are pending and examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 1, 5 and 7 recite "MHC class II ligand". It is unclear if a "MHC class II ligand" is restricted to only ligands which engage MHC class II or if MHC class II ligands may engage MHC class I as well as class II, such as CD2, CD28 and CD3. For purpose of examination, both alternatives will be considered.

(B) Claims 1, 4 and 6 recite "CD4, LAG-3, and derivatives thereof". The metes and bounds of "derivatives thereof" is unclear. Neither the specification nor the claims provide a limiting definition of "derivatives thereof" and it is unknown if said derivates encompass structural alterations to CD4 or LAG-3, or if said derivates encompass the entirety of CD4 and LAG-3 with additional molecular substituents.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 7 are drawn to composition comprising tumor cells transfected with a MHC class II ligand. Claim 2 embodies the cell of claim 1 wherein the MHC class II ligand is a "derivative" of CD4 or LAG-3.

Claims 3, 5 and 9 are drawn to processes dependent upon the identity of the MHC class II ligand. Claims 4 and 6, embody the methods of claims 3 and 5 wherein the MHC class II ligand is a "derivative" of CD4 or LAG-3.

Claims 1, 2 and 7 encompass a genus of MHC class II ligands, wherein members of said genus are not limited in terms of structure or function, because an MHC class II ligand encompasses proteins such as CD2, CD28 and the T-cell receptor, all which bind to the MHC class II complex. It is noted that the proteins which interact with any of CD2, CD28 and the T-cell receptor are activated by completely differing proteins within the class II complex, such as LFA-3 or B7. It is recognized in the art that CD4 and LAG-3 are structurally related, however, none of the other MHC class II ligands are structurally similar, nor are they functionally the same as evidenced by their interaction with distinct proteins in the MHC class II complex. Thus the genus of MHC class II ligands is highly variant. The disclosure of CD4 and LAG-3 do not provide an adequate written description of the genus because the genus encompasses molecules which differ both in structure and function from CD4 and LAG-3. Thus, one of skill in the art would reasonable conclude that applicant was not in possession of the claimed genus. It logically follows that method claims dependent upon a genus of products which have not been adequately describe are also lacking adequate written description.

7. Claims 7-9 a rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treatment, does not reasonably provide enablement for methods of prevention. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

Claim 7 specifies that the pharmaceutical composition prevents a pathological condition involving an antigen specific immune response. Claim 9 is drawn in part to a method of preventing a pathological condition involving an antigen specific immune response. The specification is not enabling for prevention. The specification has not taught how to identify individuals who will develop the pathological condition involving an antigen specific immune response, or the precise time to begin the treatment before the onset of the disease. The instant cells and methods would cause an up regulation of the immune response and the elimination of cells expressing cell expressing non-self antigens as indicated in the Table, which includes HIV, SV, HCV, HBV, CMV, HHV, HTLV-1, listeria, mycobacteria, plasmodium etc and oncogenes. It would not be possible to predict which patients will be exposed to HIV, SV, HCV, HBV, CMV, HHV, HTLV-1, under conditions that would cause the onset of the disease except for the disclosed treatment, nor would it be possible to predict when said exposure would occur. The specification has not provided evidence that the administration of the claimed cells transfected with the DNA encoding CD4 or LAG-3 would produce memory T-cells to the claimed cell effect for a lasting prophylactic immune response. Further, the specification is not enabling for predicting which patients will develop a particular type of cancer, such as breast carcinoma, melanoma or leukemia, nor does the specification teach how to predict when the cancer would occur such that the instant method can be carried out for prophylactic protection. The specification states on page 9, lines 1-2 that the anti-cancer vaccine may be inoculated to populations at high risk identified by their genotype. However, this is not enabling for when the vaccination should occur before the onset of disease. For example, the specification contemplates that the vaccine may be used to prevent leukemia (page 8, lines 12-13). The art recognizes that leukemia is a clonal disease arising from a single cell (abstract of Jacob et al, Indian J Cancer. 2002 Jun;39(2):61-5 and the abstract of Mauro et al, Curr Opin Oncol. 2001 Jan;13(1):3-7). This would require administration of the claimed compositions prior to the (9:22) translocation and resultant production of the constitutively activated bcr-abl tyrosine kinase. The art teaches that autosomal folate-sensitive fragile sites in chromosomes may increase the risk for haematologic malignancies through a complex mechanism which remains to be clarified

(abstract of Kolialexi et al, Anticancer Res. 1998 Jul-Aug;18(4A):2359-64). However, the art provides no specific means of predicting when the (9:22) translocation will occur in any given subject. The abstract of Dorak et al (Leuk Lymphoma. 1994 Jan;12(3-4):211-22) teaches that out of 112 patient with CML, those who developed the disease when aged less than 35 years (early-onset group) had higher homozygosity rates for the DOA1, HSP70 and C4 alleles of the DR53 group of ancestral haplotypes, for a subtype of HLA-A3, and a higher allele frequency of BfFb compared to the late-onset group. The oldest patient (n = 13) homozygous for DR53 was 52-years-old (p = 0.004), and all HLA-A3 homozygous patients (n = 4) were in the early-onset group (p = 0.01). The relative risk for early-onset CML yielded by HLA-A3 homozygosity was 17.6 and the HLA-identical sibling frequency was increased only in the early-onset group ($p < 0.01$). The abstract of Bortin et al (Blood. 1987 Jul;70(1):227-32) teaches that the frequency of Cw4 was elevated in patients with acute lymphoblastic leukemia (relative risk = 2.01, P less than 0.0003), acute myelogenous leukemia (relative risk = 2.06, P less than 0.0002), and chronic myelogenous leukemia (relative risk = 2.14, P less than 0.0008) and suggests that Cw3 and Cw4 may be markers for leukemia susceptibility. Thus, although homozygosity for DR53 is associated with earlier onset of CML, and the presence of Cw3 and Cw4 may indicate a greater susceptibility to leukemia in general, there are no teaching enabling one of skill in the art to predict when the (9:22) translocation will occur in any patient. Further the abstract of Haas et al (Nature. 1992 Oct 1;359(6394):414-6) teaches that in individuals harboring the (9:22) translocation, the translocated chromosome 9 was of paternal origin, whereas the translocated chromosomes 22 were derived exclusively from the maternal copy, in 11 cases with reliable polymorphisms. The abstract teaches that this provided evidence that imprinting phenomena may play an important role in acquired tumour-specific chromosome rearrangements. Thus, the factors governing the predisposition to a (9:22) translocation are complex, and cannot be accounted for simply by the inheritance of a mutant gene. There is no guidance in the specification for determining the appropriate time prior to the development of CML to begin the claimed treatment or for identifying patients at risk for developing CML.

The specification states on page 9, lines 2-3 that the vaccine may be administered to patients at high risk of relapse following surgery. However, the claims are not limited by this specific embodiment.

The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the broadly claimed invention as it pertains to "prevention".

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2 and 7are rejected under 35 U.S.C. 102(b) as being anticipated by the abstract of Makni et al (J Immunol. 1991 Apr 15;146(8):2522-9) or the abstract of Azuma et al (J Immunol. 1992 Aug 15;149(4):1115-23).

Claim 1 is drawn to a tumor cell transfected with a DNA encoding for at least on MHC class II ligand. Claim 2 embodies the method of claim 1 wherein said at least one MHC class II ligand is selected from the group consisting of CD4, LAG-3 and derivatives thereof. Claim 7 is drawn to a pharmaceutical composition comprising a pharmaceutically acceptable vehicle and cells transfected with DNA coding and expressing at least one MHC class II ligand.

Makni et al disclose the Jurkat leukemia cell line transfected with CD2, which is a MHC class II ligand according to the broadest interpretation of the term MHC class II ligand as set forth in the rejection under 112, 2nd paragraph above. Claim 2 is included in this rejection because the specification and the claim fails to set forth a limiting definition of "derivates thereof" which would exclude CD2. Claim 7 is also included in this rejection because the recitation of an intended use does not confer patentable weight on the claimed product.

Azuma et al disclose YT2C2, a human NK leukemia cell line, which expresses the CD28 differentiation Ag. The CD28 antigen is a MHC class II ligand because it is mostly expressed on CD+4 T-cells and interacts with B7 which is part of the MHC class II complex.

The reference does not disclose the transfection of a tumor cell with the DNA encoding CD28, however, claims 1 and 7 are product by process claims. Thus, the disclosure of the YT2C2 leukemia cell line which expresses CD28 would fulfill the specific embodiments of claims 1 and 7 because the claimed product would be the same as that produced by a transfection of a leukemia cell line with the DNA encoding CD28. Claim 2 is included in this rejection because the specification and the claim fails to set forth a limiting definition of "derivates thereof' which would exclude CD28. Claim 7 is also included in this rejection because the recitation of an intended use does not confer patentable weight on the claimed product.

Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Altenschmidt et al (Clin Cancer Res. 1996 Jun;2(6):1001-8)

Claim 7 is drawn to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and cells transfected with DNA encoding and expressing at least one MHC class II ligand.

Altenschmidt et al disclose naïve rat and mouse lymphocytes transfected and expressing a DNA encoding a chimeric protein comprising an extra cellular tumor cell recognition domain linked to the zeta chain of the T-cell receptor, thus fulfilling the specific embodiment of DNA coding for at least one class II ligand as the T-cell receptor is a ligand for MHC class II.

10. Claims 5-8 are rejected under 35 U.S.C. 102(b) as being anticipated by the abstract of Baron et al (Eur J Immunol. 1994 Aug;24(8):1933-6) .

The specific embodiment of claim 7 is recited above.

Claim 5 is drawn to a process for preparing cells transfected with DNA coding for at least one MHC class II ligand comprising removing cells from a patient, transfecting said cells with a DNA encoding at least one MHC class II ligand, and recovering the transfected cells. Claim 6 embodies the process of claim 5 wherein the MHC class II ligand is selected from the group consisting of CD4, LAG-3 or a derivative thereof.

Baron et al disclose a method for preparing cells expressing CD4 comprising removing CD4-CD8+ T cells from beta 2-microglobulin-deficient mice and transfected said cells with human CD4. Claims 7 and 8 are also included in this rejection because the recitation of an intended use does not confer patentable weight on the claimed product.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 5-7 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Altenschmidt et al (Clin Cancer Res. 1996 Jun;2(6):1001-8)

Claim 5 is drawn to a process for preparing cells transfected with DNA coding for at least one MHC class II ligand comprising removing cells from a patient, transfecting said cells with a DNA encoding at least one MHC class II ligand, and recovering the transfected cells. Claim 6 is drawn in part to the process of claim 5 wherein the MHC class II ligand is a "derivative" of CD-4 or LAG-3.

Claim 9 is drawn in part to a method of treating a pathological conditions involving an antigen-specific T-cell mediated immune response comprising administering the pharmaceutical composition of claim 7 to a subject in need thereof.

Altenschmidt et al teach the specific embodiment of claim 7. Altenschmidt et al do not specifically teach the removal of the naïve lymphocytes from a patient of the administration of the transfected lymphocytes to a subject in need thereof, although Altenschmidt et al suggest that the method can be used for cancer treatment with autologous T cells.

It would have been prima facie obvious at the time the claimed invention was made to remove naïve lymphocytes form patients, transfect said lymphocytes with DNA encoding a chimeric T-cell receptor comprising an extra cellular tumor cell recognition domain linked to the zeta chain of the T-cell receptor, and administering the transfected cells back to the patient. One of skill in the art would have been motivated to do so by the suggestion of Altenschmidt et al that the method be adapted for autologous lymphocytes for cancer therapy.

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 7 and 8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 9 of U.S. Patent No. 5,874,250. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 7 and 8 are obvious over claim 9 of the '250 patent. Claim 9 of the '250 patient is drawn to an isolated host cell transformed with the vector of claim 9, which embodies the DNA of claim 6. The DNA of claim 6 encompasses the DNA encoding the entirety of LAG-3 as it specifies a peptide having the recited amino acid sequences.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/18/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER